

Monday, July 8, 1991

OPENING REMARKS

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Good afternoon. I'm Judy Braslow, Director of the Division of Organ Transplantation. We are delighted you are here. We've spent the last 15 months preparing for this Surgeon General's workshop. It's required a great deal of time, planning, and assistance from many people, from staff in the Division of Organ Transplantation, staff in the Office of the Surgeon General, and commitment from the HRSA Administrator, Dr. Robert Harmon. Dr. Harmon has been the HRSA Administrator since February 1990. Previous to coming here, he was the Director of the Missouri Health Department, and prior to that, he was the county health officer in Maricopa County. While at HRSA, he's spent a great deal of his time and energy improving relationships between State and county health departments and the Federal Government. He has been of enormous support to the Division of Organ Transplantation. Without his support we wouldn't be doing this workshop today, and so it is my pleasure to introduce to you Dr. Robert Harmon.

Robert Harmon, M.D., M.P.H.
Administrator
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Thank you, Judy, and welcome. I bring you greetings from the Health Resources and Services Administration. We are very honored to have this opportunity to be part of the Surgeon General's Workshop on Increasing Organ Donation.

HRSA was created in 1982, and is one of eight agencies that comprise the U.S. Public Health Service. We've been given the leadership responsibility in promoting access to health care services for medically underserved populations, and for special populations, such as the homeless, persons with HIV infection, and persons who need organ transplantation. HRSA is composed of four bureaus, all of which focus on developing community-based health resources which will improve access for those populations in need.

The Division of Organ Transplantation is located in our Bureau of Health Resources Development. It has worked long and hard to bring to the attention

of the public and health care professionals the need for more organ and tissue donors. In conjunction with the Office of the Surgeon General, the Division has brought together leaders in the field to tackle the issue of increasing donation. HRSA is working closely with Secretary Sullivan, Assistant Secretary for Health Dr. James Mason, the Surgeon General, and the PHS agencies, in this important task.

I would like to introduce to you the Surgeon General. Dr. Antonia Novello is the fourteenth Surgeon General of the U.S. Public Health Service. She was sworn in on May 9, 1990. She entered the PHS in 1978 after practicing pediatrics and nephrology in the private sector. Prior to her appointment as the Surgeon General, her PHS career was spent at the National Institutes of Health, where she served in various capacities, eventually becoming the Deputy Director of the National Institute of Child Health and Human Development. In that position, she directed extramural programs and coordinated pediatric AIDS research. Also while at NIH, Dr. Novello was detailed to the Senate Committee on Labor and Human Resources, where, as a legislative fellow, she worked with Sen. Orrin Hatch and was directly involved in drafting the National Organ Transplant Act of 1984. I'm sure most of you are aware of the significant impact of this legislation. From the Transplant Act, we have the Organ Procurement and Transplantation Network and the Scientific Registry. These two programs provide the basis for most of the transplant activities in this country.

Dr. Novello is acutely aware of the need for more organ donors and has seen first hand the impact of renal disease in children. Among the major public health issues that are brought to her attention, she has singled out the need for more organ donors as a major priority. In Dr. Novello, the transplant community has a dedicated, outspoken advocate. I know she is committed to seeing that your recommendations receive maximum attention, both in the Public Health Service and by the general public. Please welcome the Surgeon General of the U.S. Public Health Service, Dr. Antonia Novello.

Antonia C. Novello, M.D., M.P.H.
Surgeon General of the U.S. Public Health Service
U.S. Department of Health and Human Services

Good afternoon, dear colleagues and friends. Welcome. Thank you for committing yourself to working on this important issue.

This is the second Surgeon General's Workshop on Organ Donation. The first was held in June 1983. There has been considerable change in these 8 years. We can acknowledge that and still know that we need to accelerate progress. There is no question in my mind of the urgent need to address organ donation.

Today we need to reach all Americans, but especially members of minority groups, and convince them of the value of organ donation. We need to allocate the donated organs in the most effective and efficient way, and with due respect for these gifts of life.

We need to get to the American public and convince them that organ donation saves lives, in some cases lives of their friends and families. We need to honor the needs of both: the donor and the recipient of these gifts of life.

Organ donation is a complex medical issue that cannot be considered in isolation from social issues. Organ donation must be considered with a sophisticated awareness of the racial, ethnic, religious, and educational diversity of this country.

Those of you present today represent a broad cross-section of professionals and individuals committed to increasing the supply of organs and tissues for transplantation in this country. I urge you to bring your insights and your cultural sensitivities into play, so that as we listen to one another we can come up with sound recommendations.

Whether you are a transplant recipient, a surgeon, a nephrologist, a nurse, an organ procurement specialist, a health policy analyst, a teacher, a student, or a lawyer, I urge you to bring and share your own personal knowledge and perceptions regarding organ donation. You know a great deal about other people of similar backgrounds. Bring all that awareness, all that knowledge, and all that sensitivity to the discussions, so that we can all benefit from it.

I cannot talk about the issue of organ donation as Surgeon General without being aware of my minority heritage and my professional life as a pediatric nephrologist. We may not agree on every point, and depending on our background, we might have to take practical realities into account. But there is no question that we all agree on the importance of organ donation. Few issues reach so far into the human heart.

Although many of the issues related to organ donation might be called technical, we must not disregard the issues of the heart and soul. I want you to draw on your own experiences, I want you to look into your heart. This is an issue where we need to try and understand the most serious human realities: life and death.

Since we will be concentrating on problem issues -- and I intend to drive you hard in this meeting -- I think we can take just a moment to celebrate progress.

I know many of you here today contributed to magnificent improvements in the field of transplantation. I want to acknowledge that.

For example, in the past 8 years we have seen the number of patients receiving kidney transplants almost double from 5,358 in 1982 to 9,560 in 1990, and the number of patients receiving dialysis for end-stage renal disease increasing from 65,000 in 1982 to 125,000 in 1991.

Eight years ago about 100 patients had heart transplants, while last year about 2,085 procedures were performed at 150 hospitals across the country.

At a pioneering transplant center at the University of Pittsburgh, 62 liver transplants were performed in 1982, and last year 2,656 transplants were performed.

We've also seen major changes in legislation. We have landmark legislation combining all organ procurement and transplant activities into a single national network. There is Federal assistance for organ procurement organizations, increased coverage and reimbursement for heart and liver transplants, and extensive legislation requiring hospitals to incorporate the option of organ donation into routine practice. Breakthroughs in immunosuppressive therapies, donor screening, organ preservation, and techniques to diagnose rejection have also brought improved graft survival rates for over 15,000 patients who had transplants in 1990.

Now having said all this, I must turn all of us to reality.

There are over 23,000 patients on lists today, waiting to receive an organ. Before this workshop is over, at least another 50 transplant candidates will be added to the list. Some will receive a transplant and go on to live a near normal and productive life. Others will not be so fortunate.

Each of you here today has a responsibility. Each of you has been assigned to one of seven workgroups depending upon your area of expertise and/or interest. You will be asked to discuss some very specific issues, develop recommendations, and come up with sound strategies for implementation.

We're not going to avoid the hard issues. We're not here for that. We're going to confront head-on some serious controversies and address complex technical problems, such as the importance of matching, of living donors, of informed consent -- and I mean truly informed consent.

We're going to talk about money -- about the policy of stopping payment for immunosuppressants after 1 year or continuing to finance immunosuppressive drugs for longer than that. We're going to face the truth about high rejection rates, about dialysis versus transplantation survival, and even about the risks/benefits of either dialysis or transplantation. We're going to talk about educating health care workers, particularly those in emergency rooms, so that they can be both committed and comfortable in talking to grieving relatives about

organ donation. We'll be thinking about how and when is the right time to talk to families of donors and indeed when and how to talk to prospective donors themselves.

We have a priceless opportunity in this workshop to make major changes for the good.

I want all of us to give our best while we are here. You have very hard work ahead of you.

Thank you.

Tuesday, July 9, 1991

CURRENT ISSUES IN DONATION AND TRANSPLANTATION

Dr. Novello: Good morning. I am pleased to see that you are ready for action. We have 2 days to address the issues and draft recommendations. We have a terrific sense of urgency to accomplish all of this.

Transplants started in 1954. We have almost 40 years of experience, and with it we have a climate of acceptance. For the most part, people are willing to donate. But they need to be reminded that only people can donate for people.

It is clear that the field of organ transplantation continues to develop. The goal of this workshop is to increase organ donation, particularly donation from minority groups. This workshop also gives us the opportunity to look back and to anticipate the future of organ transplantation.

Today we have better ways to prepare and preserve organs, better matching procedures, and better immunosuppressive treatments. Cyclosporine was approved by FDA in 1983, and today FK506 appears very promising. Through research, the future will bring tolerance induction, genetic engineering, and xenotransplantation.

We have learned to transplant portions of organs, such as split livers and portions of lungs. A new procedure permits the recovery of kidneys from non-heart beating donors. Today, tissues and organs can be obtained from virtually every person who dies. We are close to an artificial pancreas, and as genetically engineered tissues become a reality, to other artificial organs as well.

We have the possibility of using animal organs in some future cases. We may have new gene therapies for diabetes and lung diseases. We have made progress, but we have also created some serious problems.

Revised

In 1986, Congress required that hospitals receiving Medicare and Medicaid funds establish a written protocol to identify potential organ donors. By April 1989, 43 States and the District of Columbia had enacted legislation for this required request.

Nevertheless, written donor agreements account for a very small fraction of today's donor pool, perhaps only 3 percent of all organ and tissue donations. Although they may be valuable as a notice to families of the individual's preference and commitment to donate, surgeons still routinely require family approval. Reasons for this include the fear of legal liability and respect for grieving relatives.

Taking all of this into account, the fact remains that we might not only have an absence of donors, we might have an absence of askers as well. Too many people are not receiving the organs they need and too many people go unasked for organs they can donate. It is estimated that based on age, cause of death, and other criteria, that as many as 14,000 of the 2.2 million Americans who die every year could donate life-saving organs to those on waiting lists. A recent report noted that in 1990, 2,206 people died while waiting for organs. As I stated earlier, while we are here today, about 50 more people will be added to the transplant list. The process is never ending.

Let me briefly review the history of organ transplantation so we can put the issue in its true perspective.

In 1984, Congress passed the National Organ Transplantation Act. This required the Secretary of Health and Human Services to contract for an Organ Procurement and Transplantation Network with a private, non-profit entity. In 1986, the Secretary awarded the contract to the United Network for Organ Sharing (UNOS) with the understanding that all transplanting hospitals, when participating in Medicare and Medicaid, must become members of UNOS. UNOS, in turn, maintains the Nation's computerized list of individuals waiting for organ donations. For the first time in this country, the Transplant Act and the contract with UNOS created an equitable and efficient national system of tracking organ donations and transplantation.

As of mid-June, there were almost 19,000 patients waiting for kidney transplants; 2,000 waiting for a heart transplant; almost 1,500 waiting for a liver; 171 waiting for a heart/lung transplant; almost 600 waiting for a pancreas; and nearly 500 waiting for a lung transplant. About 12 percent of these will need a repeated transplant.

We also know that approximately half of those on waiting lists are between the ages of 19 and 45, and over 90 percent are between the ages of 19 and 64. About 40 percent are women and 60 percent are men.

✓ Each year about 15,000 whole organs from 4,500 donors are transplanted at 261 transplant centers, with the help of 69 organ procurement organizations. We have come a long way, but something is interfering with the momentum.

✓ Approximately 2,000 new patients are added to the list of those already waiting for organs each month. Sadly, between a third to a half of all Americans on transplant waiting lists will die before a transplantable organ is found.

✓ The recommendations generated by the National Kidney Foundation in February gave us points for discussion and innovative strategies to consider solutions. The participants emphasized obtaining organs from living donors and examined the issue of presumed consent, concluding that it is not yet ready for acceptance in this country. In addition, Medicare payments for the life of a transplanted organ was discussed for those patients who have no other insurance.

When we look at the issues from the Kidney Foundation meeting, and remember the article in the June 1st New York Times, which reported the successful transplantation of the small intestine in three children and two adults, a medical first, we realize once and for all that we do have important issues to consider in this workshop.

✓ The issues, no matter what they are, intertwine: the relative importance of matching and the need for minority donors; and the appeal for scarce organs to be used in the community of origin and the imperative of finding the best possible match.

✓ There are difficult decisions to be made. Which patient should receive a given organ -- the patient with the most urgency or the patient with the best match? Should live organ donations be given only to those with economic means? If there were more organ donations, and organ availability for all, some of these issues would vanish.

In the absence of that, we have issues of money and social status which we must review. The United States has come a long way in assuring that lack of money is not a barrier to organ transplantation -- but have we come far enough, and should it be reevaluated in today's world? Although nearly all kidney transplant candidates are reimbursed by Medicare, those who are not may find costs prohibitive. The estimated cost of a kidney transplant is \$51,000. Furthermore, the Medicare program only covers the cost for immunosuppressive drugs for the first year after transplantation, and those drugs may cost as much as \$3,000 a year. Many patients, especially minorities, might find this cost too high. Worries about lifelong cost of immunosuppressive drugs can cloud their relief at having an organ transplant. We must work at removing this disincentive.

There are also co-insurance and deductible requirements which can substantially limit access to kidney transplants. Can you imagine what happens with other organ transplants?

Are transplant patients really able to go back to work? Can they start paying for their immunosuppressive drugs when Federal funding stops after one year? Is one year enough to rehabilitate, and if not, do we need to readdress this issue in detail?

We must look at socioeconomic status and disease -- poverty breeds disease and often limits care. How does this affect the need for organ transplantation? Let me illustrate. I don't think we have to document the link between minority status and low socioeconomic status at this meeting. The risk of end-stage renal disease among blacks is four times higher than for whites. The prevalence is also higher. Blacks make up approximately 12 percent of the U.S. population, yet in 1987 they accounted for 27 percent of the patients with end-stage renal disease. Although blacks have an increased prevalence of hypertension and diabetes, the increased incidence of end-stage renal disease among blacks versus other minorities cannot be attributed to any one cause. The 1989 Report of the Department of Health and Human Service's Office of the Inspector General stated that there were problems in equitable distribution of organs. For instance, the report found that blacks on kidney waiting lists waited almost twice as long as whites for a first transplant: 14 months compared to 8. Patients at some centers waited as long as 18 months while at others they waited less than 6 months. Thirty percent of those waiting were black, yet only 23 percent of cadaver kidneys went to blacks. The report also said that in 1988, only about 8 percent of all cadaver kidney transplants were from black donors. Since most donors are white, whites were more likely to have a better chance at matching.

These problems can be found in other minority groups as well. For adult Native Americans living in the U.S., the overall risk of end-stage renal disease is approximately three times higher than for whites. We don't know much more about renal disease and Hispanics. One study of Hispanics in California showed a risk about the same as whites, but a study in Texas reported a three times higher risk of end-stage renal disease in this population. To make things more complicated, what we refer to as "Hispanic" is really a number of different genetic groups and, therefore, the antigens among Latino subgroups may vary, making matching more difficult.

In 1985, HCFA indicated that for blacks the percentage of end-stage renal cases was larger than the percentage of transplants. A smaller percentage, however, had transplants from living donors. Even in the presence of this bleak picture, some black families are not willing to give permission for the donation of even one cadaveric organ. Is this small percentage of donations due to cultural or religious patterns, educational levels, or basically the way these families are approached? We need to address this.

You will be hearing from experts pertaining to this issue. Some of the reasons cited for this have been religious objections, fear that organs will be taken before the person is dead, a desire to spare the departed more suffering, fear of mutilation of the body or a desire to bury the body intact, or even distrust of the medical system as a whole. Is it part of the consequence of minority status to be more fearful of exploitation? Is it that the one who asks for the donation is not cognizant of the minority individual's cultural sensitivities, or is not perceived as understanding such sensitivities? Would it help if the person raising the issue of donation was black or Hispanic? Probably so, and all these issues must be discussed.

✓ We know that a higher socioeconomic status and a higher level of educational attainment allows individuals to be willing to talk about organ donation. What we do not know is whether other groups, including minority groups, would be more willing if they were approached in a more culturally sensitive and compassionate manner. We must address this as well.

Throughout medicine and biomedical research, we have made assumptions that are increasingly being questioned. For instance, there is an assumption that minorities are less likely to comply with medical regimens or less likely to donate organs. Truth or prejudice? We all must look at this.

Look dispassionately at the issues that affect minority donations and minority transplants. Differences in ABO blood groups, the major histocompatibility-complex antigens, inadequate financial coverage, the knowledge that transplant outcomes in blacks might be worse than in whites, the presence of cultural barriers and countless other factors -- these affect the rate of transplantation but might not be the whole problem. These issues have to be factored into the discussion but are not to be used as scapegoats to avoid looking further into other issues.

We know that there are racial differences in the distribution of major histocompatibility-complex antigens. The racial differences in ABO blood groups and phenotypes also make it more likely that a candidate for transplantation will receive a well-matched kidney from a member of the same race; however, we must not be limited by this. We have overcome less than perfect matches with the advent of better immunosuppressant drugs, but research must continue in this field.

These are undoubtedly issues we have to interpret for potential donors and their families, and these are some of the barriers we need to overcome in order to increase donations from minority groups -- issues I expect to be thoroughly discussed and skillfully addressed in this meeting.

Consider for example, the standards for brain death and the need to communicate these standards to a desperately grieving relative. Should we remove this

definition altogether, as it confuses the public, or explain it more sensitively to the ones in need?

I want this group to consider everything that will increase donation, not only donations from biologically related family members but also those "related" through marriage, friendships, and strong emotional ties.

Discuss the well recognized use of living donors for kidney transplantation, and explore the practice as it relates to liver, pancreas, and lung transplantation.

Also, don't be afraid to discuss and list the hidden costs associated with being a living donor -- not just surgery, but the added cost of health insurance and time lost from work. Consider as well the need to think about presumed consent and the potential legal issues attached to this.

As Surgeon General, I cannot talk about this issue without being aware of my Hispanic heritage and my professional life as a pediatric nephrologist. We may not always agree on every point, and we have to take practical realities into account, but there is no question that we agree on the importance of organ donations and the fact that there was never a better time, or a better team, to help implement your recommendations and move the field forward.

Although many of the issues related to organ donation are technical, many are issues of the heart and soul, no matter how we disguise them. In the next 2 days, I want you to draw on your own experience and look into your own heart. Organ donation is an issue where we need to try and understand the most sophisticated medical knowledge and the most serious human issues, and translate them into action.

We need to continue to look at education of the public to encourage organ donation. In doing so, we must face hard issues, such as how many tissues and organs should be obtained from one donor and then be transplanted? How do we assure the public that their specific donation request will be honored?

What about AIDS, hepatitis, and other infectious diseases? The FDA, under the auspices of Dr. Mason, is setting a process in motion to address this problem.

What limits are there on donors -- how old and how sick can they be? Should children and babies donate organs? How do we address these ethical issues?

We must also address the issue of what constitutes informed consent. How should people be protected against pressure to be a living donor? Can they be protected, or is the natural stress in a family when a member is dying beyond control? Should we hesitate to ask? Should we routinely ask? We know that some countries such as Norway have 50 percent of their organs donated by living donors, and nearly 100 percent in Japan.

We need to look at the large picture. Can the transplant networks be improved? How do we educate health professionals, particularly those who work in emergency rooms or intensive care units, to regularly and compassionately talk with surviving relatives about organ donation? When is the right time? Who is the right person?

I urge you to focus on increasing organ donation in this country, particularly minority organ donation. I urge you to develop strategies suggesting how these recommendations might be implemented for all those in need.

Today your primary assignment is to develop recommendations. Tomorrow morning your chief assignment will be to develop strategies. In both of these tasks, please be as specific as possible and indicate which agencies, both public and private, need to be involved in the implementation.

Keep in mind that your recommendations will be shared with the individuals and organizations in charge of implementing them, such as health care professionals, private institutions, and non-profit organizations, as well as many levels of Government. Do not let that repress you. Speak candidly about the issues.

Once you present me with the recommendations, I will review them with the Advisory Committee over the next few months and work with the Division of Organ Transplantation to develop the report from the workshop.

We will publish the valuable background papers prepared for this meeting, as well as the relevant recommendations and implementation strategies proposed at this workshop. After this, the Advisory Committee that helped plan this workshop will continue to provide guidance in implementing the recommendations and strategies, and will monitor the field progress in carrying out such tasks.

I've been using a motto: "Good Science, Good Sense," since I've been Surgeon General. Rarely has my motto been so appropriate as at this workshop. Before me, I see the best people in the field of transplantation. Before us is the challenge of drafting the agenda for organ donors and recipients for the next millennium. The possibility of saving future lives makes it all worthwhile.

Thank you.

OVERVIEW OF WORKSHOP AND CHARGE TO PARTICIPANTS

Ms. Braslow: Thank you, Dr. Novello. This morning I want to show you where the Department is on some of the key issues related to transplantation and how your work at this meeting will fit into that context.

An important project is the release of center-specific data. In the transplant amendments of 1990, Congress asked us to provide to the public, information related to center-specific survival rates. We've received a lot of comment about this. Institutions are concerned that if the Government releases the information, it won't be interpreted correctly. It is not, however, a judgment call on our part. The Congress has told us that this is what we are going to do. We have to find the most acceptable and meaningful way to release this information. We've worked very closely with the Scientific Advisory Committee of UNOS. We've brought in a group of consultants and people from the Health Care Financing Administration, which had lead responsibility for the Mortality Data Report. If you recall, the first time HCFA released those data several years ago, it caused a major storm, so we thought we could learn from their experiences. We've discussed it with the UNOS Board, and we are now moving ahead.

We are trying to have a few variables that will distinguish one center from another and one kind of transplant from another. The variables were determined by the organ-specific subcommittees of the UNOS Scientific Advisory Committee. In 1991, we will look for kidneys. We will model the data so that we look at "first" vs. "subsequent" transplant, race, and cadaveric vs. living-related donors. There will be two time points: 3 month survival and 12 month survival.

For liver, the criteria will be age, the medical status at the time of transplant, and 3 and 12 month points in time. For heart, it will be first vs. subsequent transplant, the medical status of the individual at the time of transplant, congenital vs. all other disease categories, and 1 and 12 month points in time. For pancreas, we're looking at first vs. subsequent transplant, and also at the recipient category. We will want to know whether it was a simultaneous kidney/pancreas transplant, just pancreas, or pancreas transplant following a kidney transplant. For pancreas, it will be a 3 and 12 month data point as well. That data will be delivered to HRSA by UNOS near January 1, 1992. Then the Department will decide how that data will be released.

Another important concern, as Dr. Novello has indicated, is the recent case of HIV transmission through transplanted organs. The UNOS Board appointed a committee to study recommendations of a DHHS workgroup established to examine issues of HIV and other communicable disease transmission in relation to organ and tissue transplants.

As a result of our deliberations, we are suggesting that there be a pre-transplant HIV serology. We are not suggesting that the transplant be held up while awaiting results, but should the patient develop HIV, we want to know if that patient was seropositive. The workup 2 or 3 months prior to transplant routinely has an HIV serology; however, we want one immediately prior to transplant.

Secondly, we want post-transplant serologies at 6 and 12 months, which will cover the window period for almost 99 percent of patients. When HIV is identified in the post-transplant follow-up, we want it immediately reported to the UNOS Scientific Registry Data System. That allows us to identify other individuals who received organs from the same donor. Obviously, all donors are screened and we are very confident that the organ procurement agencies and transplant centers are doing a good job of donor screening. Their job is limited, however, by the sophistication of the tests available. Because that window period exists, it's important that we know when somebody is HIV positive post-transplant so that we can identify individuals who received organs from the same donor. And it's important that we receive immediate reports of AIDS and HIV-related death of a transplant recipient. We have asked UNOS to develop a system for how they're going to identify those individuals and what actions they will take when a red flag is raised. These are the HIV testing guidelines that we have begun to put in place, and I'm pleased with the response we've received from the transplant community.

There is a national effort that I think is very exciting, and we're interested in receiving your reaction to it. The Association of Organ Procurement Agencies decided about a year ago to begin a national campaign and contracted with an advertising agency to develop the campaign. At the Association's annual meeting a few weeks ago, the results of that effort were released. For the first time we had an effort that has been bought by virtually all the organ procurement agencies in this country which have agreed to adopt this slogan, "Be an organ donor, it's the chance of a lifetime." They will be using this on billboards and brochures throughout the country in their donor education and awareness efforts. You have copies of these materials. Please look at them. We're very interested in your reaction.

Now, let's get to the major task for these 2 days: developing recommendations on how to increase organ donation in the United States and developing strategies suggesting how these recommendations might be implemented. Each of you is assigned to one of seven workgroups, focusing on a specific topic related to donation. Each workgroup is to develop a set of recommendations on how to increase organ donation from the perspective of its specific focus. Today your primary assignment is to develop recommendations. Tomorrow morning your chief assignment will be to develop specific strategies and to indicate which agencies, both public and private, need to be involved in their implementation.

The seven issues fall into three categories: public education, including the general public, minority groups, and children; the health care environment, including regulatory practices and professional education; and reevaluating donor criteria, including those used for cadaveric donors as well as live donors.

The groups addressing public education will zero in on the issues related to conducting a national campaign. Group I will make recommendations with the

general public in mind. How should such a campaign be structured? Group I–B will also help answer that question by recommending ways to increase donation among individuals from various cultural backgrounds. What unique barriers need to be overcome before minorities will feel equally as interested in donation? Group I–C will focus on children, youth, and young adults, an important component of a public education campaign because they are often the most receptive to the idea of donation. Establishing their beliefs at a very young age will help insure that donation is acceptable to them now and in their adult life. Most important, children are often catalysts for educating parents about important public health issues.

Groups II–A and II–B will focus on the health care environment in which donation is likely to occur. The first group has one of the hardest tasks: examining the regulations, laws, and policies that shape the practices of health care professionals involved with donation, and making recommendations for improvement. This group will need to decide if new laws and regulations are needed or whether we should make better use of the instruments that are already available.

Group II–B will hone in on the measures necessary to educate the various health care professionals directly or indirectly involved with the donor process, assessing current educational efforts, and recommending future programs.

The last two groups will focus on the actual criteria for donation. One will discuss criteria for cadaveric donors, both adult and pediatric. It seems we must expand the limits of traditional donor criteria in order to obtain more organs for transplant. Much discussion and some research has focused on expanding the upper and lower age limits for cadaveric donors. Besides expanding the age criteria, what traditional medical contraindications can be reexamined in hopes of increasing the number of donors? Is there an acceptable gray zone for diabetics or donors with histories of hypertension, drug abuse, or less than perfect organ function? What research needs to be done in order to assist the transplant community in reaching a consensus on these criteria? By transplanting these marginal donors, are we jeopardizing the recipient's chance for a healthy recovery?

The final workgroup will focus on issues surrounding the use of live donors for transplantation, not just clinical issues of donor suitability, but also ethical and legal concerns. We want you to consider not only donations from biologically related family members, but those related through marriage, friendship, and other emotional ties. We want you to discuss the well recognized use of live donors for kidney transplant along with the practices that relate to liver, pancreas, and lung transplantation.

You have all received background papers which are to serve as catalysts for your discussion. However, do not feel limited in your discussion by the points that

have been made in the background papers. Please make your recommendations as specific and realistic as possible. Those recommendations must be implemented by health care professionals, private institutions, non-profit organizations, and many levels of Government.

Our final charge is that you speak candidly about the issues before you.

Again, our sincere thanks to all of you.

INTRODUCTION OF DR. M. ROY FIRST

Dr. Novello: Our speaker is Dr. Roy First, who is Professor of Internal Medicine and Director of the Section of Transplantation in the Division of Nephrology and Hypertension at the University of Cincinnati Medical Center. He graduated from medical school at the University of Witwatersrand in Johannesburg in 1966. After completion of his military service, he did his internship and residency at the Johannesburg General Hospital. This was followed by a fellowship in nephrology which was done at Michael Reese Hospital in Chicago, Illinois. He was appointed to the staff of the University of Cincinnati Medical Center in 1974. He has been active in the field of transplantation over the past 15 to 20 years, and has become a national and international authority in the field. He is the immediate past President of the American Society of Transplant Physicians. He has over 120 manuscripts and 13 book chapters published in the transplant literature. In addition, over 140 of his abstracts have been presented at the national and international transplant meetings.

The topic of today's address by Dr. First is "Transplantation in the Year 2010." Obviously, this is a highly speculative topic, but I can think of no one more suitable than Dr. First to give this address.

DONATION AND TRANSPLANTATION: WHERE WILL WE BE IN 2010?

M. Roy First, M.D.
Professor of Medicine
Division of Nephrology and Hypertension
University of Cincinnati Medical Center

Dr. Novello, ladies and gentlemen, it is indeed a pleasure and a privilege to be here today. The talk I've been asked to give this morning, transplantation in the year 2010, is obviously very speculative. I thought we should look at where transplantation has come to the present time, and then speculate some about the future. If we look at the current 1-year survival rates for first transplants (Table 1 - this data was recently published by UNOS for all 1988 transplants for which

12 month follow-up is available), we can see that the results have reached an all-time high: patient and graft survival for living-related donor kidneys are 97 and 91 percent, respectively; for cadaver kidneys, 92 and 81 percent; for pancreas, 89 and 71 percent; for liver, 76 and 69 percent; for heart, 83 and 82 percent; for heart/lung, 57 percent; and for lung transplantation, 48 percent. The last two are in their infancy relative to the other organ transplants, and I'm sure that over the next decade we'll see substantial improvements in heart/lung and lung transplant results.

Over the past 8 years, transplantation has grown, and as you're all aware, last year over 15,000 solid organ transplants were done in the United States, a record number (Table 2). Of these, 9,560 were kidney transplants. There were over 2,600 liver transplants, 2,085 heart transplants, and a large growth in pancreas transplantation, which reached 549 last year, largely due to the pioneering efforts of Dr. Sutherland in Minneapolis.

With these excellent results, and the increased number of transplants, what is the problem? The problem is why so many experts are here today. The problem is one of organ donation. The UNOS organ transplantation waiting list released last week has over 23,000 people on it. Of major concern are the deaths of those on this waiting list. In 1989, almost one in three potential heart transplant recipients died while waiting. Almost a quarter of those awaiting a liver transplant died. The figures out for 1990 reveal that there were 2,206 deaths of patients on the waiting list. This translates to over six a day: every 4 hours, one patient on the waiting list for solid organ transplantations is dying.

TABLE 1.
ONE YEAR SURVIVAL RATES FOR FIRST TRANSPLANTS IN 1988 *

ORGAN	PATIENT SURVIVAL	GRAFT SURVIVAL
KIDNEY (RELATED DONOR)	97%	91%
KIDNEY (CADAVER DONOR)	92%	81%
PANCREAS	89%	71%
LIVER	76%	69%
HEART	83%	82%
HEART-LUNG	57%	57%
LUNG	48%	48%

* Data from UNOS report

TABLE 2.
SOLID ORGAN TRANSPLANTATION IN THE UNITED STATES
1982-1990

	1982	1983	1984	1985	1986	1987	1988	1989	1989
KIDNEY	5,358	6,112	6,968	7,695	8,975	8,967	9,123	8,706	9,560
LIVER	62	164	308	602	924	1,199	1,682	2,164	2,656
HEART	103	172	346	719	1,368	1,438	1,644	1,700	2,085
PANCREAS	35	61	87	130	140	142	242	419	549
HEART-LUNG	0	20	22	30	45	41	71	68	50
LUNG							32	119	262

I have some numbers, supplied by Dr. Alan Hull, on kidney acquisition per million population per year from a number of different countries (Table 3). If we look at roughly the middle of the decade of the '80s - '84 and '85 - we can see that the figures for the U.S. reveal that organ acquisition in this country was on a par with many European countries (Table 4). Nevertheless, organ acquisition in the U.S. still lags far behind the leaders of Western Europe: Belgium has 41 kidneys per million population per year; and Austria, where laws of presumed consent are actively applied, has over 52 kidneys per million population per year.

What are some of the possible solutions to the dilemma of organ donation and distribution? (Table 5) There's no question in my mind that the major issue remains improved professional and public education. This meeting is going to go a long way towards improving the public knowledge about what is needed in this country with regard to organ donation. The recently published report of the Office of the Inspector General notes that there is a paucity of minority donors in this country. This is another area that needs to be actively pursued, especially considering that approximately 30 percent of the patients on the waiting list for kidneys are black. Relaxed donor criteria need to be looked into further. The recent increase in organ donation last year is largely a result of the use of donors who may not have been accepted in the past, largely older donors, and I think this is an area that's going to be addressed at this meeting and has been addressed in the past by my colleague from Cincinnati, Dr. Wesley Alexander.

The question of the use of non-heart beating donors prior to obtaining consent also has been raised recently. Increasing the number of donors by using living, unrelated donors; the whole question of improved application of the routine request; and the possibility of going to routine referral of potential organ donors -- all need to be considered. Presumed consent, while effective in many European countries, probably would not be acceptable in this country to the general public. One area that has been discussed extensively over the past year has been the question of financial incentives to donor families, and I personally think that this is an area that deserves further study. And finally, research into xenotransplantation so that animal organs may be used to overcome the shortage is something that one might look at in transplantation 20 years from now.

So where are the future directions that I see transplantation going? (Table 6) First, a number of new immunosuppressive agents are on the horizon. Some have been used in laboratory animals with excellent results; others have been used in clinical studies with very impressive and exciting results. Over the next 5 years, we will hear a lot more about many of these drugs. To complement this, a number of new monoclonal antibodies are on the horizon and should be released in the next few years. Beneficial effects also have been shown by drugs that affect the prostaglandin-thromboxane system.

TABLE 3.
KIDNEY TRANSPLANTATION WORLDWIDE 1989 *

COUNTRY ¹	CADAVER KIDNEYS ²	KIDNEYS TRANSPLANTED	
		CAD	LRD (% TOTAL)
<u>EUROTRANSPLANT</u>			
BELGIUM (9.9)	41.3	409	
AUSTRIA (7.5)	52.1	391	
W. GERMANY (60.5)	30.5	1,847	
LUXEMBOURG (0.37)	16.2	6	
NETHERLANDS(14.8)	24.4	361	
<u>SCANDINAVIA TRANSPLANT</u>			
SWEDEN (8.4)	34.5	290	81 (22)
NORWAY (4.2)	20.0	84	76 (48)
DENMARK (5.1)	25.3	129	18 (12)
FINLAND (5.0)	29.2	146	39 (17)
<u>INDEPENDENTS</u>			
FRANCE (56.2)	33.8	1,900	57 (3)
ITALY (57.4)		604	10.5
U.K. (60.9)	28.4	1,732	122 (7)
USA (248.8)	27.5	6,844	1,862 (21)

* Data from Hull, A.

¹Country and population (in millions)

²Cadaveric kidney retrieval rate in number of kidneys per million population per year

TABLE 4.
 KIDNEY ACQUISITION IN THE DECADE OF THE EIGHTIES*
 (MILLION POPULATION/YEAR)

COUNTRY	AUSTRIA	BELGIUM	FRG	NETHERLANDS	FRANCE	USA
YEAR						
80	12.5	16.7	12.0	16.7	12.3	
81	15.2	15.7	13.7	22.0	13.0	
82	18.7	14.0	15.0	22.1	15.8	16.0
83	14.4	19.5	16.2	23.6	16.7	18.6
84	29.9	20.8	20.0	25.9	17.5	22.4
85	27.6	21.3	20.4	18.8	21.0	24.6
86	30.9	26.8	25.8	25.7	24.0	29.5
87	42.5	37.4	26.0	28.6	29.0	29.0
88	39.0	38.0	26.9	25.5	32.5	29.1
89	52.1	41.3	30.5	24.4	33.8	27.5

* Data from Hull, A.

TABLE 5.
POSSIBLE SOLUTIONS TO THE DILEMMA OF
ORGAN DONATION AND DISTRIBUTION

1. Improve professional and public education
2. Train minority requestors
3. Relax donor criteria
4. Use of non-heart-beating donors
5. Use of living unrelated donors
6. Routine request and routine referral
7. Presumed consent
8. Financial incentives to donor families
9. Xenotransplantation

Other future directions involve the question of: 1) cellular transplantation, 2) small bowel transplantation, 3) tolerance induction, 4) xenotransplantation, and 5) genetic engineering. These are the areas that are going to receive attention in the next 10–20 years. For the remainder of my talk, I want to focus on each of these 5 areas.

First, cellular transplants. Islet cell transplantation has been successful in animals. In humans, amelioration of diabetes has been incomplete or transient, and there's a need for multiple islet donors for a single recipient. Some of these problems are related to the fact that the islets are exquisitely sensitive to biophysical or immunological injury when they are separated from the pancreas. An interesting attempt to overcome this problem has been the recent report and development of the biohybrid perfused artificial pancreas, which is designed to incorporate islet tissue and a selectively permeable membrane that isolates this tissue from the immune system of the recipient. This device is reseedable through silicone rubber ports in the event the islets must be replaced periodically. Work on this perfused artificial pancreas by the group in Boston, led by Tony Monaco, was reported recently in *Science*. A vascular graft, made of PTFE, is incorporated into the circulation in the experiments in dogs in much the same way as an arteriovenous shunt. This vascular graft is surrounded by a housing device and then a hollow fiber membrane. The pancreatic islets are inserted through the seeding port and are separated from the circulation by this hollow fiber membrane. This hollow fiber is of a size that allows glucose to pass

through to stimulate the islets; it allows insulin to pass through in the other direction, and also allows nutrients to reach the islets. However, it prevents lymphocytes and antibodies from getting through to the transplanted, or the seeded, pancreatic islets. Using this device, they were able to keep dogs euglycemic without any need for insulin and no immunosuppression for up to 6 months. This is certainly something that's going to warrant future consideration, and might well play a role in the treatment of the many diabetics with and without end-stage renal disease.

There are a number of areas where cellular transplants have been used, for example, in Parkinson's disease. In Parkinson's disease, there is selective destruction of the dopaminergic neurons of the substantia nigra of the brain. The cells of the adrenal medulla release dopamine, and clinical trials have been done utilizing either adrenal medullary autografts (taking the person's own adrenal medulla), and fetal neural tissue grafts into the caudate nucleus. Reports on this research come from Mexico and Scandinavia, and are somewhat conflicting; some showing significant improvement in the neurological symptoms of Parkinson's disease; others have not been that impressive. But certainly this is a fertile area for future research on the use of cellular transplants.

Next, small bowel transplantation, which is in its infancy, and has had only a few cases described. In small bowel transplantation, predominant problems are: acute and chronic rejection, graft vs. host disease, diagnosis of rejection, and the digestive and non-digestive functions of the small bowel graft. In experimental animals, the use of FK506 has been shown to prevent acute rejection and the fatal graft vs. host disease. A few isolated clinical papers show excellent results, and of these, the most prominent come from Toronto. There, patients have survived almost 2 years with normal bowel functions. Excellent results also come from Pittsburgh and other centers. The successful clinical results have occurred with vigorous pre-treatment of the donor with monoclonal and polyclonal antibodies to the donor of the small bowel, and in very vigorous immunosuppression of the recipient. In this way, it has been possible to control both the acute and chronic rejection phases, and the transfer of donor lymphocytic tissue in the graft that causes the graft vs. host disease. The application of new surgical techniques, the diagnosis and treatment of rejection, and the availability of new immunosuppressive agents, will undoubtedly result in successful transplantation of the small intestine by the year 2010.

The next area is the induction of tolerance, which is the induction of a state of antigen-specific unresponsiveness, so that an individual would be unresponsive to the particular tissues of the donor but would maintain other immune functions. Experimentally, this is possible to do in animals using donor bone marrow, anti-lymphocyte serum, and cyclosporine. In other animal experiments, conducted largely by David Sachs at the N.I.H., the use of monoclonal antibodies, whole body irradiation, thymic irradiation, and allogeneic bone marrow transplantation, have resulted in the induction of chimerism. Tolerance has also been achieved

in concordant animals against the xenogeneic barrier. In human beings, partial tolerance has been achieved in humans with post-transplantation bone marrow transfusion, as has been described by the University of Alabama in Birmingham, and with total body irradiation. In the Birmingham studies, the patients who received the donor bone marrow had far less rejection and very good outcomes when compared with the matched controls. However, this is difficult to achieve. In our institution, led by Wes Alexander, we've been studying the role of donor-specific blood transfusions in living-related and cadaveric donor transplantation. This involves taking blood from the donor, giving it to the recipient, and delaying the transplant for 12-18 hours. The early results have been encouraging, although there has been a fair amount of rejection: one graft out of about 20 has been lost.

Next is the issue of xenotransplantation, or cross-species transplantation. If this could be achieved, the successful use of animal organs for transplantation into humans could solve the organ shortage that exists. If this can be achieved through advancements in immunobiology and immunopharmacology, 20 years from now we won't have to worry about people dying due to a lack of organs. However, this will be difficult to achieve because humans have natural, or preformed, antibodies against all animal species.

Clinical xenotransplantation has been performed approximately 30 times. In some instances, the organs function for a very short while and then fail. The most recent case that comes to mind is the one in Loma Linda in which a chimpanzee or baboon heart was transplanted in a young girl for whom no donor could be found. The girl lived only a few days. Cross-species transplantation has been successful in concordant animal species, such as rodents, mice, and rats, because those are the types of animals that lack preformed antibodies against the donor. There's been renewed interest in xenotransplantation with the introduction of FK506, 15-deoxyspergualin, new monoclonal antibodies, and with tolerance induction. Xenografting has been classified into two functional groups: the concordant, or species combinations, in which the graft survives several days and rejection tends to be along classical pathways, with cellular and humoral immune mechanisms; and the discordant, where there's immediate or hyperacute destruction of the graft. This is mediated by preformed natural antibodies, the complement cascade, activation of endothelial cells lining the vessels of the donor organ, and platelet aggregation. Attempts have been made to achieve accommodation of the xenograft so that the natural antibodies can be removed by plasmapheresis or immunoadsorption. This has been successful in the laboratory. Production of a transgenic pig, which expresses a human DAF (a molecule that inhibits activation of C3 and C5) also has been performed, preventing activation of the complement cascade. In the third level, involving internal damage and platelet aggregation, models have used the platelet activating factor antagonists to prevent the platelet aggregation. There's a lot of experimental work going on in this field. It is conceivable that early in the 21st century, we might see clinical xenotransplantation evolving successfully.

Another very interesting model of xenotransplantation was recently described by the group in Boston. This involved prevention of the xenograft rejection by masking the donor HLA class I antigens. Rejection of human pancreatic islets and liver cells were circumvented by masking the donor antigens with W6-32, an antibody to HLA class I. This is done before transplantation of these cells under the kidney capsule of mice. In this model, the islets have functioned without immunosuppression beyond 200 days, as demonstrated by normal histology and C-peptides secretion in response to a glucose load. This might be another way to fool the immune system and prevent rejection, and to get animals and humans to accept tissues from other species.

Finally, we come to the issue of genetic engineering. Using molecular biological techniques, entire genes or groups of genes can be produced and inserted into the genome of specific cells; that is, into the genetic material of the cells. Gene alteration therapy could be used to correct metabolic diseases, leading to end-stage organ failure, or to alter the host immune response. It's very likely that 20 years from now, we'll see genetic engineering therapy aimed at changing the genes for insulin-dependent diabetes, or polycystic kidney disease, or to alter the immune response of an organ recipient to prevent rejection.

Transplantation has also been used in the treatment of genetic disease. Bone marrow and liver transplantations provide the necessary feasibility tests of gene transfer therapy for many genetic diseases. Transplantation allows for assessment of a single organ correction of a specific enzyme deficiency by the introduction of normal genes. There are a number of conditions where the basic abnormality is in a single organ due to a genetic or inherited metabolic disease (such as alpha-one antitrypsin disease, Wilson's disease, and primary hyperoxaluria), and where replacement of that organ has resulted in correction of the genetic disease. Another example of gene transfer therapy is the use of pigs as potential blood donors to humans. Copies of the human DNA that make hemoglobin are inserted into a one-cell fertilized egg from a pig. In about 0.5 percent of these cases, the DNA successfully copies itself and is inserted into the DNA of the pig. The pig then gives birth to transgenic piglets, meaning they carry the genes of both the maternal pig and the human DNA inserted into it. The offspring of these pigs permanently carry the human DNA, make hemoglobin, and pass it on to their offspring. Such pigs have a mixture of human and pig hemoglobin. The human hemoglobin can be separated and theoretically used for transfusion into humans. In much the same way, one can imagine other modifications of genes to overcome diabetes and diseases that cause liver damage, or to alter the immune system. Therefore, genetic engineering, by adding or deleting genes involved in the immune responses or by induction of tolerance, can be done at the embryonic level, leading to a transgenic strain, or at a later level by inserting a vector for DNA transfer. There are a number of different levels at which one can alter the DNA of an animal, and this may one day be true of human beings as well.

It is very likely that over the next 20 years, many of these areas will come to fruition. However, for the foreseeable future, there will be a shortage of organs, and that is going to be the focus of the next couple of days.

Once again, thank you very much for inviting me here today.

LUNCHEON ADDRESS

LOUIS W. SULLIVAN, M.D.
SECRETARY OF HEALTH AND HUMAN SERVICES

Good afternoon. I appreciate the invitation to participate in this important meeting.

Let me begin by saying to you, Dr. Novello, that I have been very impressed with your work. You have been at the forefront of the efforts to make organ transplants a reality for more Americans, particularly minority citizens. I thank you for your leadership and dedication on this vital area of national health.

I'd like to spend a few minutes discussing organ donation specifically within minority populations, and then talk about current Federal efforts to improve rates of donation and the recent successes we've seen across the country through heightened public awareness.

The sessions today paint a picture of transplantation in this country -- a picture often not as encouraging as we would like it to be. Today, almost 24,000 Americans are waiting for an organ transplant -- and little more than half are likely to receive one.

Major advances in science, medicine, and biotechnology have given us the capability and the know-how to perform successful transplants. Last October Dr. Vaughn Starnes of Stanford University, a participant in this workshop, performed the world's first single-lung transplant using a lung segment from a living related donor. In January, he successfully repeated the procedure in a one-month-old baby girl. Dr. Starnes, your work is clear testimony to the tremendous potential for transplantation. This is truly one of the wonders of medicine to replace a deteriorated vital organ with a healthy one.

But, as the Washington Post noted last week, "the biggest constraint on organ transplantation is neither technology nor cost but the shortage of available donor organs." Indeed, the number of available organs has leveled off after doubling during the 1980s, while waiting lists have continued to lengthen. Fortunately we have seen an encouraging break in this plateau -- during 1990, donation increased by approximately 11 percent, but this still falls short of the need.